Cotrimoxazole in hospitalised patients with severe COVID-19 infection compared to the standard of care – an investigator-initiated, randomised controlled trial (CoTroxCov Study)

Investigators:

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Study Coordination Centre:

School of Tropical Medicine, Kolkata

4/12/2021

Study Site:

Single-centre study recruiting in-patients at Medical College Hospital, Kolkata

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Study Sponsor:

Investigator-initiated study with a financial grant of Rupees 6 Lakhs for logistic support from Department of Health and Family Welfare, Govt of West Bengal (Refrence Number-HFW-38011(56)/7/2020-DIR-MES).

Study Rationale:

COVID-19, caused by SARS-CoV-2, is a highly transmissible disease that has caused a global pandemic. The disease is mostly self-limiting with milder form of infection, but at least 15-20% of those who are infected progress to severe disease. The case fatality, albeit at a low rate not exceeding 1-2%, is attributed to a misdirected hyperimmune response to the infection leading to a cytokine release syndrome or cytokine storm. The cytokine-mediated inflammation of the lung alveolar bed may result in ARDS and acute respiratory failure. Further, cytokine-induced hypercoagulability adds to the injury. With no evidence-based, specific anti-viral treatment yet available, the mainstay of therapy is supportive with steroids and low molecular weight heparin.

Co-trimoxazole (combination of trimethoprim and sulphamethoxazole in a 1:5 ratio is an anti-folate bactericidal agent effective against a wide range of systemic bacterial infections including respiratory tract infections. It has been around for over 80 years and is inexpensive

and readily available with a generally good safety profile. It has a rapid onset of action with excellent bioavailability and lung penetration. In addition to having antimicrobial properties co-trimoxazole has immunomodulatory and anti-inflammatory properties and may be a potential treatment option for cytokine storm syndrome mediated severe COVID-19. Cotrimoxazole acts on peripheral blood mononuclear cells and suppress TNFa secretion at clinically achievable concentrations. [1] Cotrimoxazole reduces systemic inflammation in HIV infection by altering the gut microbiome and immune activation. [2] Such immunomodulatory and anti-inflammatory properties of cotrimoxazole may account for it's potential use in rheumatoid arthritis, [3] The benefit of using cotrimoxazole in fibrotic lung disease has been reported by several researcher groups. [5, 6, 7] Against this backdrop, it is not surprising to witness off-label use of cotrimoxazole in Covid-19. It is believed, during the Covid-19 disease process, mitochondrial injury of host cells occurs leading to release of damage associated molecular patterns (DAMPs). These DAMPs stimulate formyl peptide receptors (FPRs) present on the surface of neutrophils and monocytes, leading to release of intracellular and extracellular reactive oxygen species (ROS), which then drive the cytokine storm. Cotrimoxazole is reported to block the FPRs and thus may prove beneficial by decreasing neutrophil recruitment, generation of ROS and production of pro-inflammatory cytokines. [4] The few attempts to study if cotrimoxazole therapy could prompt favourable outcome in Covid-19 have been quite promising. [4, 8]

In view of the above, we contemplate to undertake a randomized controlled trial in order to investigate if oral cotrimoxazole therapy instituted early in hospitalised Covid-19 patients could prevent transition of the disease to a critical stage.

Study Hypothesis:

Our hypothesis is that use of oral cotrimoxazole in patients with severe COVID-19 can prevent 'higher' oxygenation requirements through non-invasive and invasive mechanical ventilation, and decrease in-hospital stays as well as death rate.

Study Objectives:

Primary

To evaluate the efficacy of add-on cotrimoxazole in hospitalised patients with severe COVID-19 infection receiving standard of care, compared to only standard of care, in preventing progression to systemic hyperinflammatory status.

Secondary

To evaluate the safety and tolerability of cotrimoxazole through entire hospitalisation period, compared to the control arm, as assessed by incidence of serious and non-serious adverse events (SAEs) in addition to changes in other disease parameters like fever, SpO2, CRP and respiratory rate.

Trial Design:

CoTroxCov Study is an investigator-initiated, single-center, randomised proof-of-concept clinical trial.

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Participants:

All consecutive Covid-19 in-patients at Medical College Hospital, Kolkata who are screen-eligible and consenting participation will be enrolled.

Inclusion criteria

a. Adult individuals, age >18 and <65 years

b. COVID-19 infection documented by a positive RT-PCR test

c. Hospitalised patients with severe COVID-19 infection, characterized by
fever (at the time of screening or when admitted) and requiring supplemental oxygen through non-rebreath mask between 10L-15L/ min.

d. Clinical/radiological evidence of interstitial pneumonia requiring admission (optional)

e. Informed written consent

Exclusion criteria

a. Patients who require invasive or non-invasive (including CPAP and high flow nasal cannula) ventilation at the time of inclusion.

b. AST/ALT values >5 fold the ULN.

c. Documented impairment of renal function

d. Absolute neutrophil count below 500 cells/mm^3

e. Absolute platelet count below 50,000 cells/mm^3

f. Documented sepsis or high suspicion of superimposed severe bacterial or fungal infection

g. Comorbidities or concomitant medications likely to be incompatible for cotrimoxazole use

h. Pregnancy or lactation.

i. History of cotrimoxazole hypersensitivity

j. Patients participating in another clinical trial for SARS-CoV-2 infection

Intervention and Comparator:

The intervention group, cotrimoxazole plus standard of care, will receive oral cotrimoxazole 960 mg three times daily for 7 days. Treatment with drugs or procedures in routine clinical practice that the clinician responsible for the patient deems necessary is allowed. The control group will receive drugs or procedures in routine clinical practice according to the best standard of care as per local protocol.

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Main Outcomes:

Primary Outcome Measures

a. Mean change in clinical status assessment using the 7-point ordinal scale at day 7 after randomisation compared to baseline (Score ranges 1-7)

1. Death;
2. Hospitalised, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3. Hospitalised, requiring non-invasive ventilation or high flow oxygen devices;
4. Hospitalised, requiring supplemental oxygen;
5. Hospitalised, not requiring supplemental oxygen - but in need of ongoing medical care (COVID-19 related or otherwise)
6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (independent)
7. Not hospitalised

b. Duration of hospitalisation: Days from the date of enrolment to the date of discharge

c. Number of in-patient deaths

Secondary outcome measures

1. Changes in body temperature, respiratory rate, CRP, SpO2
2. Incidence of serious and non-serious adverse events

Randomisation:

Randomisation to treatment arms cotrimoxazole plus standard of care or standard of care in a 2:1 ratio will be performed by the Chief Investigator - I, using a table of random numbers, an internet-based randomisation tool. After checking that all inclusion criteria are met and none of the exclusion criteria, the Chief Investigator - I will communicate the recruiting investigator the assigned treatment.

Blinding:

This study is open, un-blinded.

Sample Size:

200 patients of COVID-19 moderate-to-early severity infection who require hospitalisation: 134 will receive cotrimoxazole plus Standard of Care and 66 will receive Standard of Care.

Trial Commencement and Duration:

The Protocol version number is 2, as of 24th December 2020. The recruitment shall commence hopefully from 9th February, 2021. Recruitment is anticipated to be completed by 9th May 2021. The Study is expected to be completed by end-May 2021.

4/2/2021

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Ethics Compliance:

The Study has institutional ethics committee approval (Medical College and Hospital, Kolkata IEC Ref No: MC/KOL/IEC/NON-SPON/863/01/2021)

Trial Registration:

This trial is in the process of being registered in the Indian Clinical Trials Register, provisional CTRI Number CTRI/ 2021/02/040567 and Universal Trial Number U1111-1264-5128.

4/2/2021

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Informed Consent Form

Study Title: **Cotrimoxazole in hospitalised patients with severe COVID-19 infection compared to the standard of care – an investigator-initiated, randomised controlled trial (CoTroxCov Study)**

Protocol Version: 01 Subject's Initials: .....Subject's Name:.....
Subject No: ..... Date of birth/ Age: .....

Statement	Subject's initial /LTI in each box
I confirm that I have read and understood the information sheet dated ..... for the above study and have had the opportunity to ask questions.	[ ]
I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reasons, without my medical care or legal rights being affected.	[ ]
I understand that the investigator, others working on the investigator's behalf, the Institutional Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information revealed to third parties or if published.	[ ]
I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).	[ ]
I agree to take part in the above study.	[ ]

Name of Subject _____ Subject's Signature (or Left Thumb Impression) _____ Date _____

Name of Legally Acceptable Representative (LAR) _____ LAR's Signature (or Left Thumb Impression) _____ Date _____

Investigator's statement / Statement of person administering Informed Consent

I, the undersigned, certify that I have fully and carefully explained all relevant aspects of this research study, to the subject signing this consent and it appears that he/ she has reasonably understood the nature, risks and potential benefits, if any, of his/ her participation in this study. If applicable, I confirm that I have explained the nature, purpose and foreseeable effects of the study to the subject's legally acceptable representative, whose name is documented above, and that he/ she has agreed on the subject's participation in this study. The LAR has confirmed to this by his/ her personally dated signature.

Name/Signature of Investigator _____ Name/Signature of Person administering IC _____ Date _____

----------Use the following only if applicable----------

If this informed consent document is read to the subject because the subject is unable to read the consent form, an impartial witness must be present during the informed consent administration procedure and must sign the following statement: I confirm that the information in the consent form was accurately explained to, and apparently, understood by the subject. The subject consented free of will, to take part in this research study.

Name of Impartial Witness _____ Signature of Impartial Witness _____ Date _____

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